



PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
John A. Copland, III
Slavisa Gasic
Randall J. Urban
Melvyn Soloff

Group Art Unit: 1646

Examiner: Nguyen, Q.

Atty. Dkt. No.: UTSG:239/SHS

Serial No.: 09/418,095

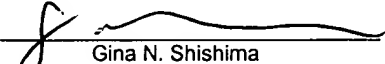
Filed: October 14, 1999

For: THIAZOLIDINEDIONES IN
COMBINATION WITH OTHER
THERAPEUTIC AGENTS FOR TUMOR
THERAPY (Amended)

CERTIFICATE OF MAILING
37 C.F.R. § 1.8

I hereby certify that this correspondence is being deposited with the U.S. Postal Service as First Class Mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on the date below:

1/15/01
Date


Gina N. Shishima

DECLARATION OF GINA N. SHISHIMA

I, Gina N. Shishima, hereby declare as follows:

1. I am a patent attorney registered before the United States Patent and Trademark Office.
2. I understand that the Patent and Trademark Examiner has found the claimed subject matter of the referenced application to be anticipated by the publications of Mueller *et al.* February 1998, Brockman *et al.* 1998, Elstner *et al.* July 1998, and Kubota *et al.* 1998. Claims 1-10, 16, 17, 24-29, and 33-35 have been rejected over each of these references.
3. I am submitting this declaration to establish how the publication date of Mueller *et al.* February 1998 was determined.

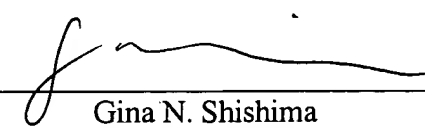
4. Mueller *et al.* was published in the February 1998 volume of the journal *Molecular Cell*. Maria Cusano, managing editor of *Molecular Cell*, provided information to me via an e-mail message dated December 20, 2000 about the February 2000 volume of *Molecular Cell*. She stated, "The printer's records show that the journal was mailed February 20, 1998. There is no record of when it went online, but the normal procedure is to post the issue online at 5:00 p.m. the evening before the mail date. My guess is that the February issue went online at 5:00 p.m. February 19."

5. I do not know of any information that suggests or indicates the journal was published in any form earlier than February 19, 1998.

6. In view of the above, I communicated to John A. Copland, a co-inventor of the above-referenced patent application, that evidence indicated the publication date of Mueller *et al.* was no earlier February 19, 1998.

7. I hereby declare that all statements made of my own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

Date: 1/12/01


Gina N. Shishima
Reg. No. 45,104

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Gina N. Shishima

DECLARATION OF JOHN A. COPLAND, III, PH.D. UNDER 37 C.F.R. § 1.132

I, John A. Copland, III, hereby declare as follows:

1. I am a joint inventor of the subject matter of all claims currently pending in the referenced patent application.
2. I am an assistant professor in the Department of Internal Medicine, Division of Endocrinology at the University of Texas Medical Branch in Galveston, Texas. I received a Ph.D. in Endocrinology from Medical College of Georgia, Department of Physiology and Endocrinology in Augusta, Georgia. I have experience in the study of thiazolidinedione and its effect on cancer cells both with and without a traditional cancer therapy. I have presented data at

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international meetings on the subject, such as the American Association for Cancer Research and The Endocrine Society. I also have several manuscripts in preparation for publication on the subject. A copy of my *Curriculum Vitae* is attached as Exhibit 1.

3. I am a citizen of the United States.

4. I understand that the Examiner of the referenced application contends that it would require undue experimentation for one skilled in the art to practice the claimed methods of inhibiting the growth of a cancer cell or treating cancer comprising contacting a cancer cell with an effective amount of a thiazolidinedione. I further understand that the Examiner has suggested that the application does not reasonably enable the use of a thiazolidinedione to treat any cancer in any and all patients.

5. I am providing this Declaration to set forth additional data I generated concerning the inhibition of the proliferation of cancer cells *in vivo* after treatment with a thiazolidinedione, troglitazone, and a chemotherapeutic, 5-fluorouracil (5-FU).

6. The data in Exhibit 2 were generated by subcutaneously injecting UMRC cells, a human renal carcinoma cells, into the trunk of 40 mice, which formed two tumors each. Five days after tumor implantation, tumors were treated daily Monday through Friday with i) troglitazone at a dosage of 500 mg/kg body weight by oral gavage and 5-fluorouracil (5-FU) at a dosage of 10 mg/kg body weight via intraperitoneal injections; ii) troglitazone alone at a dosage of 500 mg/kg body weight; iii) 5-FU alone at a dosage of 10 mg/kg body weight; or iv) neither compound. Tumor volume was measured on day 5, 10, 17, 24, and 31 after implantation. While tumor volume of mice treated with troglitazone alone or 5-FU alone was decreased compared to tumors treated with neither compound, the greatest inhibition of tumor growth was observed in mice treated with both troglitazone and 5-FU.

7. Exhibit 2 provides data demonstrating that tumors in nude mice were smaller after treatment with troglitazone and 5-FU than with either compound alone or neither compound.

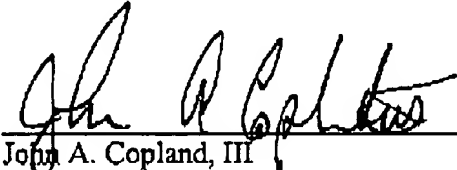
8. The Specification provides information about performing experiments with animal models, including a nude mouse. Specification, pages 39-41. It also provides details about dosages for 5-FU and thiazolidinediones. Specification, at least on page 45 and 51. This material provides enabling support for the filing of the instant declaration.

9. The information provided herein, coupled with information from the Specification and the knowledge of one of skill in the art at the time the application was filed, is evidence the claimed methods are enabled for *in vivo* applications.

10. For reasons discussed above, the application does reasonably enable the use of a thiazolidinedione and an anticancer agent to inhibit the proliferation of a cancer cell *in vivo* as a means of treating cancer.

11. I hereby declare that all statements made of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 1/12/00


John A. Copland, III



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Gina N. Shishima

DECLARATION OF JOHN A. COPLAND, III, SLAVISA GASIC, RANDALL J.

URBAN, AND MELVYN SOLOFF UNDER 37 C.F.R. § 1.131

We, John A. Copland, III, Slavisa Gasic, Randall J. Urban, and Melvyn Soloff,
hereby declare as follows:

1. We are the inventors of the subject matter of claims pending in the above-referenced patent application.
2. We understand that the Patent and Trademark Examiner has found the claimed subject matter of the referenced application to be anticipated by the publications of Mueller

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et al. February 1998, Brockman *et al.* 1998, Elstner *et al.* July 1998, and Kubota *et al.* 1998.

Claims 1-10, 16, 17, 24-29, and 33-35 have been rejected over each of these references.

3. We are submitting this declaration to set forth evidence that we invented the subject matter of the claimed invention prior to the publication dates of Mueller *et al.* February 1998, Brockman *et al.* 1998, Elstner *et al.* July 1998, and Kubota *et al.* 1998.

4. We further understand that the publication date for Mueller *et al.* is on or after February 19, 1998, as set forth in the Declaration of Gina N. Shishima (filed herewith).

5. Submitted as Exhibit 1 to this declaration are pages from the laboratory notebook of John A. Copland (Copland) documenting studies involving a thiazolidinedione and a chemotherapeutic agent and their inhibitory effect on the proliferation of a cancer cell. Page 1 of Exhibit 1 shows experiments with Saos-2 cells, an osteosarcoma cell line. In those experiments, sets of Saos-2 cells were treated in triplicate with varying concentrations of either i) troglitazone alone; ii) troglitazone and 5-fluorouracil; iii) troglitazone and cisplatin; 5-fluorouracil alone; iv) cisplatin alone; v) DMSO; or vi) nothing. Page 2 shows the amount of DNA content for each set of cells measured three days after they had been treated. Page 3 is a graph that summarizes the data compiled before the publication dates of Mueller *et al.*, Brockman *et al.*, Elstner *et al.*, and Kubota *et al.*, which showed the inhibitory effect of a thiazolidinedione and a chemotherapeutic agent on the proliferation of a cancer cell.

6. The experiments shown in Exhibit 1 were conducted in the United States by John A. Copland.

7. Prior to the publication dates of Mueller *et al.*, Brockman *et al.*, Elstner *et al.*, and Kubota *et al.*, we had contacted a cancer cell with troglitazone, which is a thiazolidinedione,

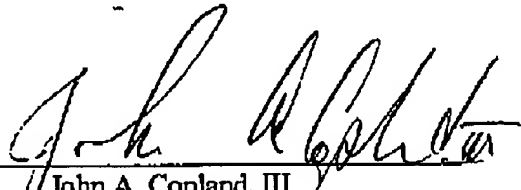
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and 5-fluoracil or cisplatin, which are chemotherapeutic agents. The DNA content of these cells was also measured prior to the publication dates of the cited art.

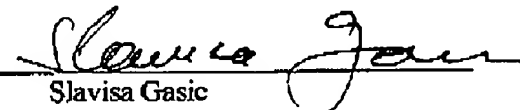
8. In view of the above, John A. Copland's notebook pages are evidence of the claimed invention prior to the publication of any of the publications of Mueller *et al.*, Brockman *et al.*, Elstner *et al.*, and Kubota *et al.*

9. We hereby declare that all statements made of our own knowledge are true and all statements made on information are believed to be true and further that the statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of this application or any patent issued thereon.

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John A. Copland, III

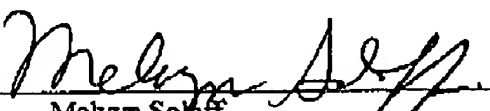
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Slavisa Gasic

Date: 1/12/01


Randall J. Urban

Date: 1/12/01


Melvyn Soff